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Stereoselective 1,4-additions

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CHAPTER 1

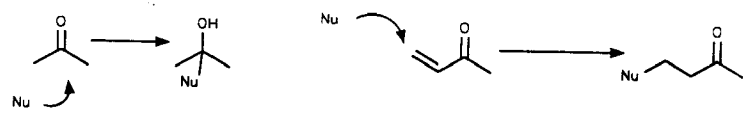
CARBON-CARBON BOND FORMATION BY ADDITIONS TO CARBONYL COMPOUNDS

§ 1.1. Introduction

Of the many known carbon-carbon bond forming reactions probably the most important are the additions of carbon-nucleophiles to carbonyl compounds.
These additions can be divided into two major reaction modes:

i) 1,2-addition and

ii) 1,4-addition (scheme 1.1.1.)



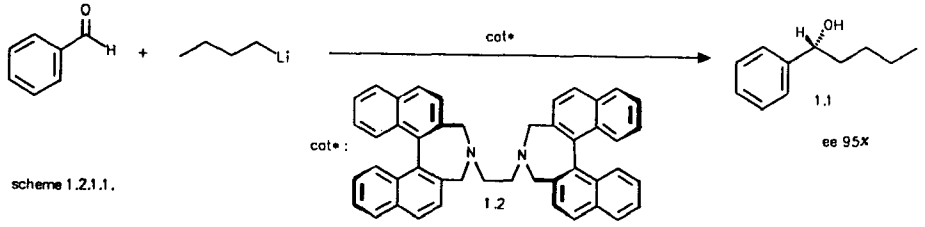
scheme 1.1.1

Both reactions have been known for more than a century and considerable progress has been made in stereocontrolled additions. This has resulted into methodology for the stereoselective carbon-carbon bond formation resulting in enantiomerically pure compounds. These enantioselective reactions will be discussed in the following sections.

§ 1.2. 1,2-Addition of nucleophiles

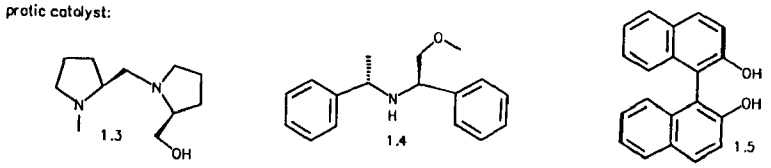
§ 1.2.1. Stereoselective addition of organometallic reagents

The most widely used 1,2-addition is the reaction of a organometallic compound with a ketone or aldehyde[1]. In 1940, Betti and Lucchi raised the curtain on enantioselective alkylation of aldehydes. The product of the addition of methylmagnesium iodide to benzaldehyde in the presence of N,N-dimethylbornylamine, obtained in 73% yield, had an optical rotation of 0.30° [2]. This result encouraged many research groups to study the addition of Grignard and lithium reagents to aldehydes, especially benzaldehyde. These efforts culminated in the successful 1,2-addition of n-butyllithium to benzaldehyde in excellent enantiomeric excess (95% e.e.) using chiral diamine **1.2** as a chiral ligand (Cram and coworkers[3], scheme 1.2.1.1).
These examples are based on the principle of modification of the organometallic reagent with modified chiral ligands. More useful is the execution of these 1,2-additions of organolithium reagents in the presence of protic chiral auxiliaries, first demonstrated in 1969[4].



scheme 1.2.1.1.

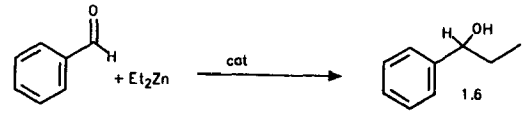
Mukaiyama and coworkers reached an e.e. of 95% in the addition of n-butyllithium to benzaldehyde using the proline derived diaminoalcohol ligand **1.3**[5]. With aminoether **1.4**, Eleveld and Hogeveen[6] achieved 90% e.e. in the same reaction. Seebach and coworkers finally obtained an e.e. exceeding 98% in the addition of phenylmagnesium bromide to 1-naphthylaldehyde using bis-β-naphthol **1.5** complexed to tris(isopropoxide)titanium chloride[7] (scheme 1.2.1.2).



scheme 1.2.1.2

In all these additions the chiral auxiliary has to be used in more than stoichiometric amounts (ranging from 1.3 to 4 equivalents). Cram[3] has found that the use of ligand **1.2** in 0.7 mol% resulted in the alcohol **1.1** with an e.e. of only 7%. A similar result was found by Hogeveen[6] using 2.4 mol% of **1.4** leading to **1.1** in 19% e.e. These results showed that there was catalytic activity but that the competing addition of achiral organolithium reagent was also fast.

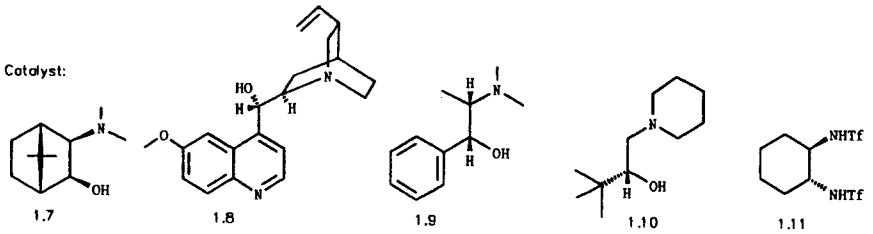
The problem that the organometallic reagent adds to aldehydes, without being activated by a chiral ligand, can be overcome using diorganozinc compounds. Diethylzinc does not react with aldehydes. Only when a suitable ligand is added as catalyst does the 1,2-addition reaction occur ("ligand accelerated catalysis"). The most studied reaction in this respect is the addition of diethylzinc to benzaldehyde (scheme 1.2.1.3).



scheme 1.2.1.3.

Oguni reported in 1984 the use of S-leucinol as chiral ligand for the diethylzinc addition to benzaldehyde resulting in 1-phenylpropanol **1.6** with an e.e. of 49%[8]. Several other catalysts were used after this initial result, for instance: DAIB **1.7** by

Noyori (e.e. up to 99%)[9]; quinine **1.8** by Wynberg (e.e. up to 92%)[10]; methylephedrine **1.9** by Buono (e.e. up to 81%)[11]; aminoalcohol **1.10** by Oguni (e.e. up to 98%)[12] and diamide **1.11** in combination with titanium tetraisopropoxide by Ohno (e.e. up to 99%)[13] (scheme 1.2.1.4).



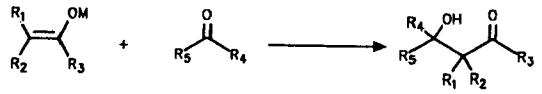
1.7 1.8 1.9 1.10 1.11

scheme 1.2.1.4.

Further insight in the enantioselective 1,2-addition of diethylzinc was obtained when Oguni and coworkers used **1.10** with a low e.e. of itself (11%) and found alcohol **1.6** with a much higher e.e. (82%)[14]. Noyori performed a thorough study of this non-linear effect using DAIB **1.7** as the chiral ligand[15]. Using 8 mol% (-)-DAIB with an e.e. of 15% he obtained alcohol **1.6** with an e.e. of 95%. From this study it was concluded that the active catalytic spieces is a dimer and the R,R- or S,S-dimers are better catalysts than the corresponding R,S dimer.

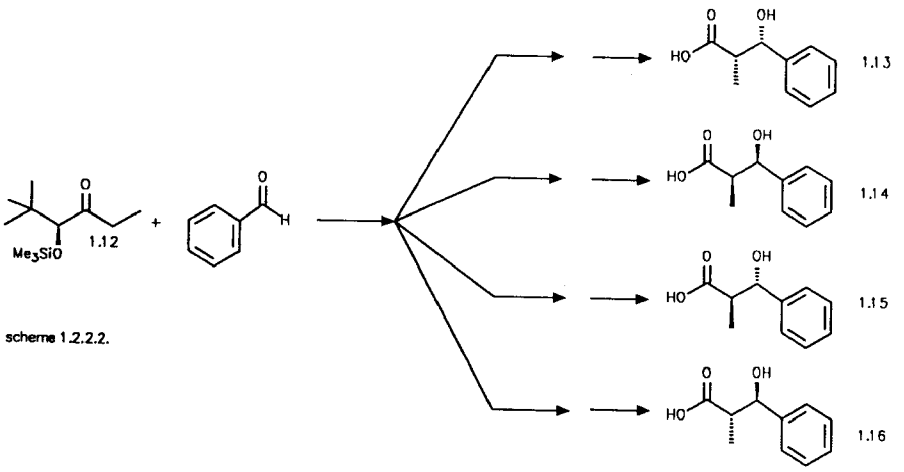
§ 1.2.2. Stereoselective addition of enolates; the aldol reaction

Enolates can also readily add to an aldehyde or ketone in an aldol condensation and numerous groups contributed to stereoselective aldol reactions[16] [17] [18]. Especially Heathcock has made a thorough study of the aldol reaction with lithium enolates (scheme 1.2.2.1).



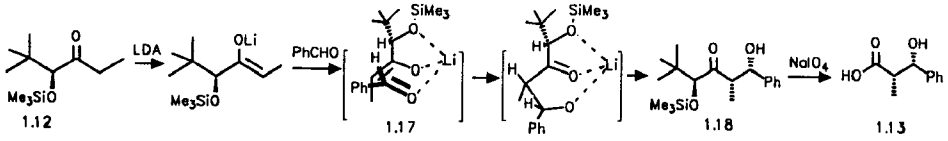
scheme 1.2.2.1.

This study[19] resulted recently in " Protocols for the Preparation of Each of the Four Possible Stereoisomeric α-Alkyl-ß-hydroxy Carboxylic Acids from a Single Chiral Aldol Reagent". The principle is shown in scheme 1.2.2.2. Starting with silyl protected α-hydroxyketone **1.12** and benzaldehyde it should be possible to obtain all stereoisomers of acids **1.13-1.16.**



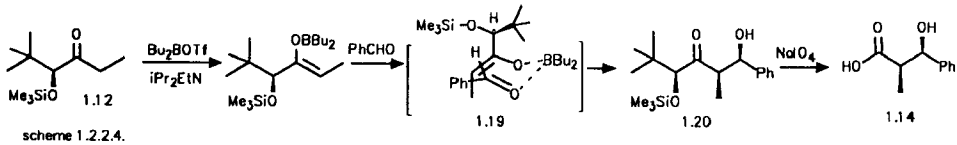
scheme 1.2.2.2.

The synthesis of **1.13** starts with the preparation of the Z-lithium enolate of chiral ketone **1.12** with LDA. This enolate adds in a stereocontrolled manner to benzaldehyde presumably via a chelated least hindered three coordinated transition state **1.17**. The syn[20] isomer **1.18** which is formed in this way was converted into **1.13** using periodate (scheme 1.2.2.3).



scheme 1.2.2.3.

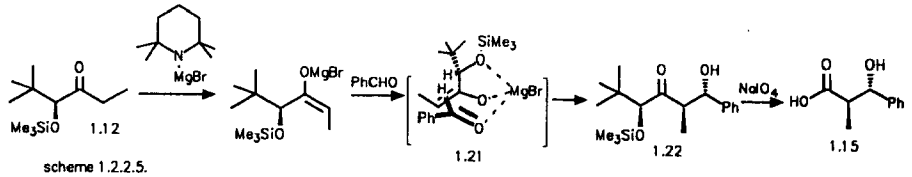
The enantiomeric syn isomer **1.14** was prepared via the borium enolate Using dibutyl borontriflate in combination with diisopropylethylamine also the Z-enolate of **1.12** is formed. The difference in absolute stereochemistry of adduct **1.20** can be explained by the fact that a dibutylboron is capable of coordinating only two oxygen atoms as is illustrated in transition state model **1.19** (scheme 1.2.2.4). Due to the dipolar repulsion between the O-B and O-Si bonds in **1.19** one conformation of the enolate is preferred. Aldol product **1.20** formed in this way was converted into **1.14**.



scheme 1.2.2.4.

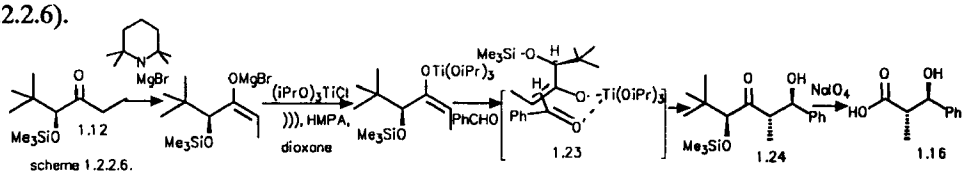
The anti isomer **1.15** was prepared by using an E-metallo-enolate of **1.12**, which is capable of coordination with three oxygen atoms, to react with benzaldehyde

(analogous to the formation of **1.13**). The magnesium ion in a magnesium enolate is capable of coordinating with three oxygen atoms but usually these enolates are obtained as a mixture of E- and Z-enolates. Only when N-(bromomagnesio)-2,2,6,6-tetramethyl-piperidine (MTMP) is used as the base the E enolate formed exclusively. Subsequent aldol reaction provides anti adduct **1.15** presumably via transition state **1.21** (scheme 1.2.2.5).



scheme 1.2.2.5.

The preparation of the enantiomeric anti isomer **1.16** was the most difficult. In analogy with **1.14** a metal had to be used which was only capable of coordinating two oxygens. For the formation of the anti adduct an E-enolate is essential. The most ideal species therefore would be the E-boron enolate, which unfortunately cannot be made from **1.12**. After many attempts they found that it was possible to trans metallate the E-magnesium enolate to the corresponding titanium enolate. It was necessary to add trisisopropoxytitanium chloride in a HMPA/dioxane mixture. The trans metallation was successful only when the reaction was performed at 25-45°C under sonication. In this way **1.16** was prepared with an e.e. of 60% (**1.13, 1.14, 1.15**, e.e.>90%) (scheme 1.2.2.6).

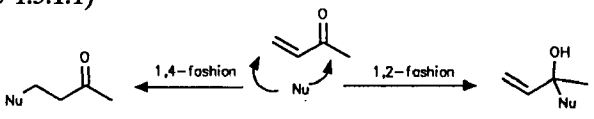


scheme 1.2.2.6.

§ 1.3. 1,4-Addition of nucleophiles

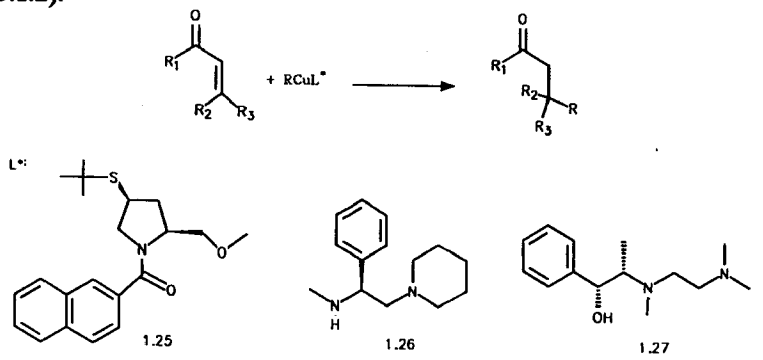
§ 1.3.1. Stereoselective addition of organometallic reagents

The 1,4-addition of organometallic reagents to an enone or α,β-unsaturated ester is similar to the addition of organometallic reagents to aldehydes (1,2-addition, § 1.2.1). The major difference is that in principle an organometallic reagent has two reaction modes with α,β-unsaturated carbonyl compounds: addition in a 1,2-fashion or in a 1,4-fashion. (scheme 1.3.1.1)



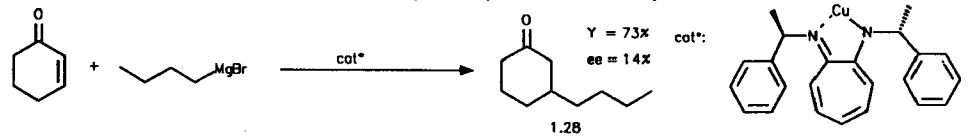
scheme 1.3.1.1.

Organolithium compounds normally react in a 1,2-fashion[21]. Organomagnesium compounds react in both fashions. Organocopper and organozinc compounds usually react in a 1,4-fashion[22] (with aldehydes organozinc compounds react in a 1,2-fashion, vide supra) . Fortunately organocopper and organozinc compounds can be made from organolithium and organomagnesium compounds. When an organomagnesium compound has to be added in a 1,4-fashion it is also possible to add a catalytic amount (1 mol%) of a Cu^{I} salt. This is due to the fact that an organocopper compound is a softer reagent and is more reactive than the corresponding organomagnesium reagent. Only a limited number of highly stereoselective organocopper mediated 1,4-additions are known. Kretchmer[23] and coworkers in 1972, using (-)-sparteine as a chiral ligand for the organocuprate, were the first to perform an enantioselective organocopper 1,4-addition. Following this work several research groups reached high enantioselectivities. Leyendecker[24] used ligand **1.25** in the addition of Me_2CuLi to chalcone (e.e. up to 94%). Dieter[25] used organo-(hetero)-cuprates (e.e. up to 83%). Rossiter[26] used **1.26** in the addition of phenylcuprates to cyclohexenone (e.e. up to 97%). Corey[27] used **1.27** in the addition of alkylcopper reagents to cyclohexenone (e.e. up to 95%) (scheme 1.3.1.2).



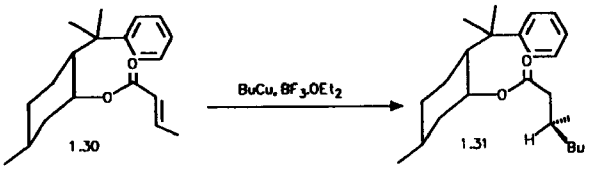
scheme 1.3.1.2

In these examples again an excess of chiral ligand was used (1.1-3.5 equivalents). The only[28] catalytic enantioselective 1,4-addition of a n-butylmagnesium reagent to an enone i.e. cyclohexenone has been described by Lippard and coworkers[29]. This reaction was catalyzed by a copper(I) complex based on an N,N'-dialkyl-substituted aminotroponeimine **1.29** as a chiral ligand. (scheme 1.3.1.3)



scheme 1.3.1.3.

Instead of using a chiral ligand or cosolvent, organocuprates have also been used in an enantioselective 1,4-addition to chiral α,β-unsaturated esters. The highest e.e. (>99%) has been obtained by Oppolzer and Löher[30] in the addition of dibutyl- and diphenyl-copper to trans 8-phenylmenthyl crotonate **1.30** in the presence of BF_3-OEt_2. (scheme 1.3.1.4)



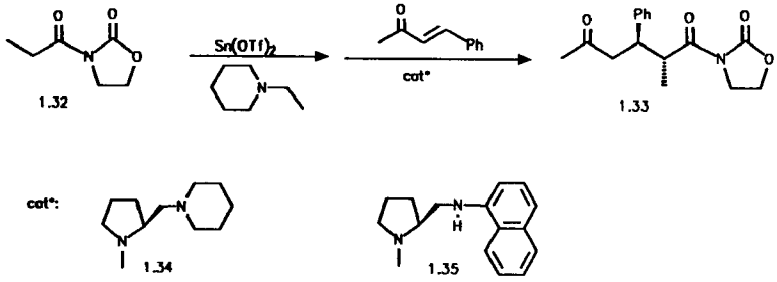
scheme 1.3.1.4. de > 99%

§ 1.3.2. Base catalyzed stereoselective addition of enolates; the Michael addition

Although there are many base catalyzed Michael additions only three different approaches have been developed for the catalytic enantioselective Michael addition:

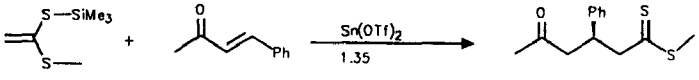
1) via metal enolates under the influence of chiral ligands;
2) using chiral amines as bases;
3) using achiral bases in the presence of chiral crown ethers.

In the first methodology, developed by Mukaiyama and coworkers[31] [32], a tin enolate is made in situ from amide **1.32**. This tin enolate reacts with an enone under the influence of an activator (trimethylsilyl triflate) and chiral amines **1.34** or **1.35** to give Michael adduct **1.33**. The enantioselectivity reached in this reaction was as high as 93% using amine **1.34**. (scheme 1.3.2.1)



scheme 1.3.2.1.

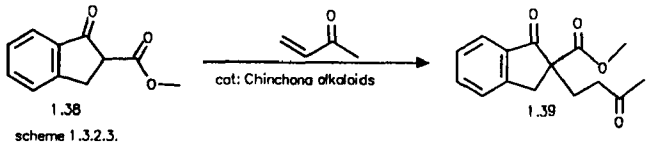
A major disadvantage of this system is the use of a stoichiometric amount of chiral amine. This can be overcome when trimethylsilyl bis-thioketene acetals, such as **1.36** are used. Only 10 mol% of tin triflate and chiral amine **1.35** are sufficient to obtain the adduct **1.37** with an e.e. of 70% [33]. (scheme 1.3.2.2)



1.36 1.37

scheme 1.3.2.2.

The second approach has been widely explored. Especially cinchona alkaloids such as quinine have been investigated. In these additions 2-carboxymethyl indanone **1.38** is mostly used as the Michael donor and methyl vinyl ketone as the acceptor to yield Michael adduct **1.39**. Långström and Berger[34] were the first to study this reaction. Mainly due to the optimization studies by Wynberg an coworkers[35] [36] an o.p. of 76% has been achieved. (scheme 1.3.2.3)

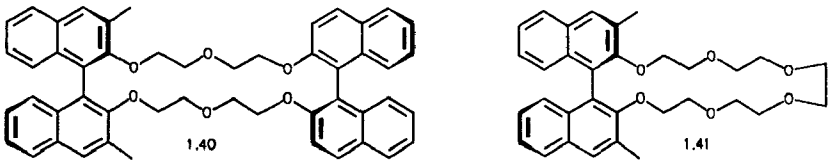


1.38 1.39

scheme 1.3.2.3.

To avoid purification problems also polymer bound catalysts based on cinchona alkaloids have been used. The enantiomeric excesses that are reached are, however, only low to moderate[37] [38] [39]. Insertion of spacer groups between the backbone of the polymer and the alkaloid improved the stereoselectivity. The highest e.e. obtained with a polymer bound alkaloid as chiral base catalyst is 65%[40].

The highest enantioselectivities in the base catalyzed Michael additions are reached via the third method which implies the use of achiral bases complexed to chiral crown ethers. Cram and coworkers[41] [42] studied the reaction of **1.38** with methyl vinyl ketone to adduct **1.39** with bases in the presence of chiral bis-β-naphthol derived crown ethers. The highest e.e. obtained, 99%, was obtained using 4 mol% of **1.40** in combination with KOtBu. (scheme 1.3.2.4)



1.40 1.41

scheme 1.3.2.4.

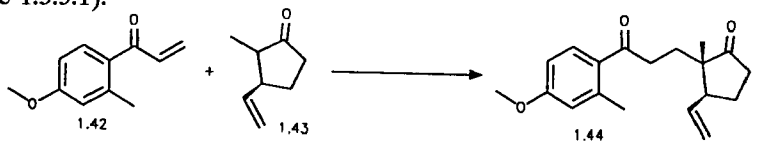
After this excellent result many chiral crown ethers were tested in the reaction of α-phenyl methyl acetate with methacrylate[43] [44] [45]. The highest e.e. obtained in this reaction (83%) was obtained using **1.41** as the chiral crown ether.

§ 1.3.3. Asymmetric Michael addition with a stereogenic center in the donor

Two major classes can be distinguished in the Michael addition in which the

stereocontrol is the result of a stereogenic center in the donor: substrate control and auxiliary control.

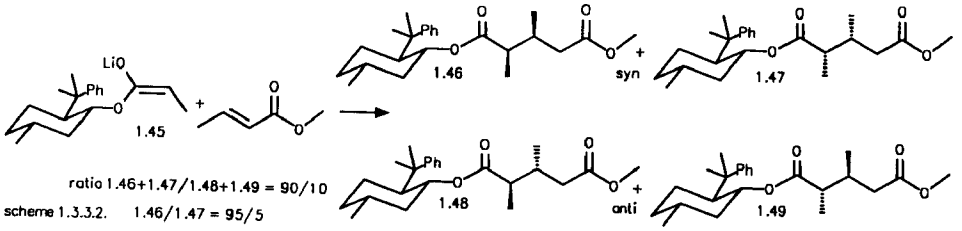
The class of substrate controlled Michael additions with a high degree of stereoselectivity is further limited to chiral cyclic enolates. The stereocontrol is mainly due to the shielding of one of the π-faces of the enolate by the ring substituent that resides at the stereogenic center. The trans stereoselective addition of the lithium enolate of **1.43** to enone **1.42** to give adduct **1.44** illustrates this principle[46] [47] [48] [49] (scheme 1.3.3.1).



scheme 1.3.3.1.

Auxiliary control has frequently been used with esters and amides[50]. An example of the auxiliary controlled addition of an ester enolate with excellent stereoselectivity, developed by Corey and coworkers, is the addition of the E-lithium enolate of 8-phenylmenthyl propionate **1.45** to E-methyl crotonate[51] (scheme 1.3.3.2).

A mixture of four diastereoisomers **1.46-1.49** was found. The syn/anti ratio of 90:10 shows the simple diastereoselectivity of this reaction. The induced diastereoselectivity is seen in the 95:5 ratio between the RS-**1.46** and the SR-**1.47** diastereoisomers. This enantioselective Michael addition was used in the synthesis of 7,20-diisocyanodociane[52].

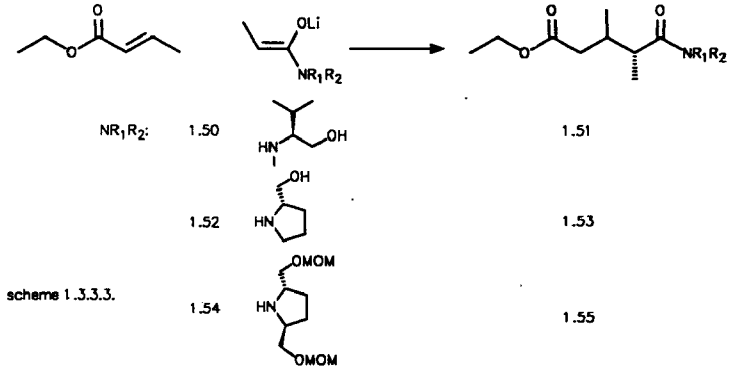


scheme 1.3.3.2.

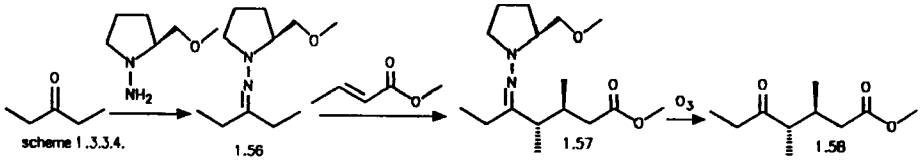
A variety of chiral amides, such as **1.50, 1.52** and **1.54**, can easily be prepared from amino alcohols that are derived from amino acids. The addition of the lithium enolates of these amides under kinetically controlled conditions to α,β-unsaturated esters yields optically active glutarates **1.51, 1.53** and **1.55**. Both syn- and anti-glutarates with diastereoisomeric excesses (d.e.'s) up to 80% can be obtained[53] (scheme 1.3.3.3).

For the stereoselective Michael addition of ketones usually a transformation into their corresponding hydrazones or imines using chiral hydrazones or amines is required. The hydrazone method has extensively been studied by Enders[54]. One example of this method is the addition of the lithium aza-enolate of chiral hydrazone **1.56** to methyl methacrylate to yield the hydrazone **1.57**. Removal of the auxiliary hydrazone

functionality occurs on ozonolysis to provide δ-ketoesters like **1.58** in approximately 40% overall yield. The stereoselectivity is high with d.e.'s and e.e.'s $\geq$ 96%. (scheme 1.3.3.4)

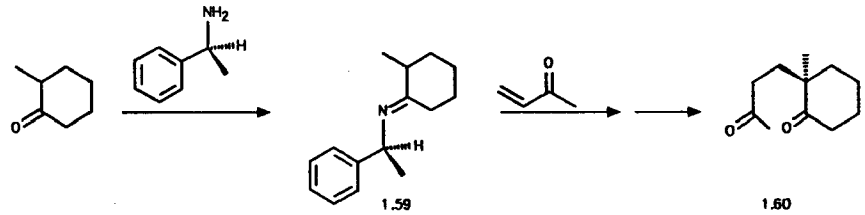


scheme 1.3.3.3.



scheme 1.3.3.4.

2-Substituted cycloalkanones can be added stereoselectively to a Michael acceptor if they are converted to their corresponding imines. Especially α-phenylethylamine has been used as chiral amine for imine formation. An example is the slow but spontaneous addition of imine **1.59** to methyl vinyl ketone from which the diketone **1.60** can ultimately be obtained in 83% yield with an e.e. of 90% (scheme 1.3.3.5). The presence of an aryl substituent α to the amine seems to be essential. This methodology has been applied in the synthesis of many natural products[55].

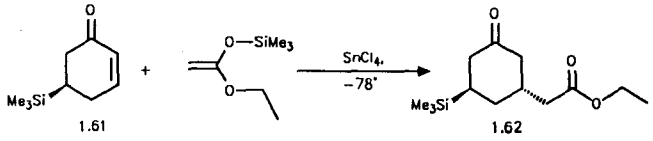


scheme 1.3.3.5.

§ 1.3.4. Michael addition with a stereogenic center in the acceptor

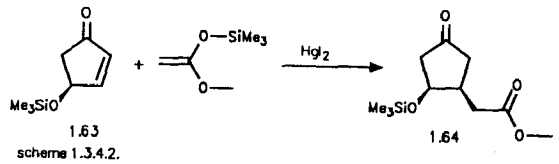
A stereogenic center at the γ-or δ-position in the Michael acceptor can control in most cases the topicity of the nucleophilic attack by steric effects. The precise reaction

conditions are important for the products that are obtained. Usually the trans adducts are obtained as is illustrated in the synthesis of **1.62** starting from **1.61**[56] (scheme 1.3.4.1).



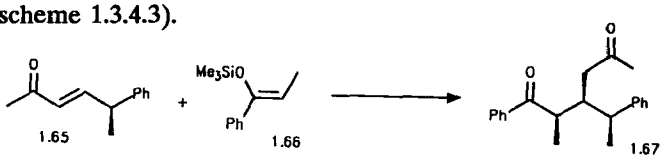
scheme 1.3.4.1.

Danishefski and coworkers[57] have however found a remarkable cis selectivity in the addition of silylketene acetals to γ-siloxy substituted cycloenone **1.63** using mercury iodide as a catalyst (scheme 1.3.4.2). This cis selectivity has been attributed to a combined effect of both the mercury iodide and the presence of an electron withdrawing silyloxy substituent.



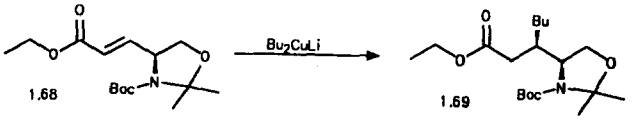
scheme 1.3.4.2.

In the acyclic series a lower stereocontrol is exerted by the γ-substituent. For instance, the addition of silyl enol ether **1.66** to **1.65** resulted in the formation of a mixture of diastereoisomers in 69% yield with syn adduct **1.67** as the main component (syn/anti: 82:18). No other syn adduct was detected whereas both anti adducts were found (12 resp. 6%)[58] (scheme 1.3.4.3).



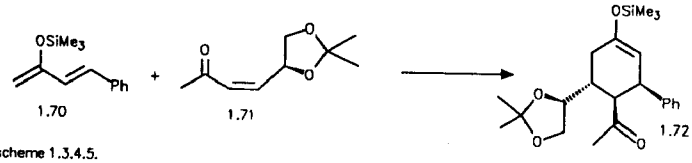
scheme 1.3.4.3.

In case the γ-substituent is cyclic and contains hetero atoms a high selectivity (up to 99%) can be reached. One example is found in the addition of a cuprate to γ-amino-α,β-unsaturated ester **1.68**. In this addition reaction both Bu_2CuLi and BuMgBr (using a catalytic amount of CuI) can be used to provide **1.69** as a single diastereoisomer[59] (scheme 1.3.4.4).



scheme1.3.4.4.

In an other example complete stereocontrol in a double Michael reaction was obtained only when Z-γ-alkoxy-enone **1.71** was used. The cyclohexanone derivative **1.72** was obtained as a single diastereoisomer in 83% yield. Using, however, E-**1.71** a mixture (62:38) of two diastereoisomers of **1.72** were obtained[60] (scheme 1.3.4.5).

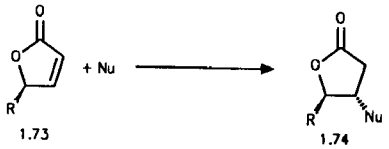


scheme 1.3.4.5.

§ 1.4. α,β-Unsaturated lactones as Michael acceptors

γ-Substituted α,β-unsaturated lactones are in principle ideal as Michael acceptors as the stereogenic center at the γ-position might dictate which π-face is shielded from the attacking nucleophile. Farina and coworkers[61] have performed many additions to racemic 5-methoxy-2[5H]-furanone, especially hetero atom nucleophiles have been used. The chiral α,β-unsaturated lactones of which we are aware[62] that have been used as Michael acceptors can be divided into two classes: the furanones **1.73** and the pyranones **1.75**.

The 1,4-addition reaction with furanones is depicted in scheme 1.4.1. Many research groups have worked on the synthesis[63] of γ-alkyl-substituted furanones and the addition reactions to these Michael acceptors. Unfortunately only dimethyl copper lithium or lithio tris(methylthio)methane have been used as Michael donors. This work was carried out by Hanessian and coworkers, who prepared six chiral lactones[64]. Only dimethyl copper lithium has been added to the three chiral furanones made by Font and coworkers[65] and to the two prepared by Kunesch and coworkers[66]. In all these examples the nucleophile added trans with respect to the substituent.



scheme 1.4.1.

Using pyranones as chiral Michael acceptors the 1,4-addition has only been studied with cuprates. The stereogenic center can reside at two places; at the γ-position as in **1.75a-c** or the δ-position as in **1.77**. We have only found four examples in this respect with a stereogenic at the γ-position. Flemming and coworkers[67] added $(PhMe_2Si)_2CuLi{\cdot}LiCN$ to **1.75a-c** (**a** R= Me, **b** Et, **c** CH_2SiMe_2Ph) and MeMgI

catalyzed by 1 mol% CuI to **1.75a**. Yoda and coworkers[68] added Bu_2CuLi and Me_2CuLi to **1.75d** (R $=NHCO_2CMe_3$). Again only the trans adducts were formed (scheme 1.4.2a).
To our knowledge there is only one example (by Yoshikoshi and coworkers[69]) of a Michael addition to a δ-substituted-α,β-unsaturated lactone **1.77**. In this case also a trans selective addition takes place to yield **1.78** (scheme 1.4.2b).

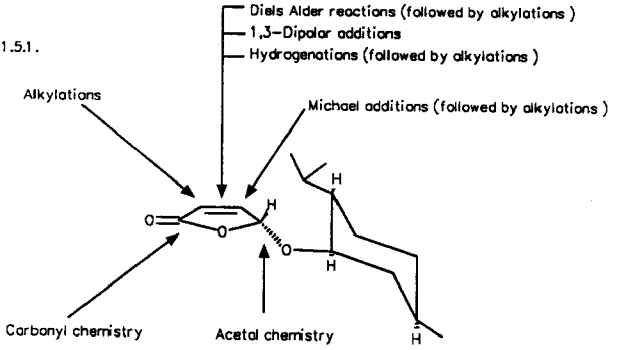
a: R = Me
b: R = Et
c: R = $CH_2SiPhMe_2$
d: R = $NHCO_2CMe_3$

scheme 1.4.2

§ 1.5. Aim of this thesis

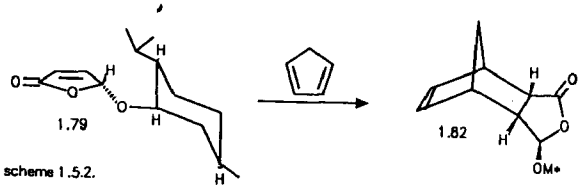
In our research group the new multifunctional synthons 5(R)-(l-menthyloxy)-2[5H]-furanone **1.79** and 5(S)-(d-menthyloxy)-2[5H]-furanone **1.80** are being developed. These enantiomerically pure γ-butenolides together with racemic 5-methoxy-2[5H]-furanone **1.81** are versatile and flexible building blocks[70]. Some of the possible reaction modes are depicted in scheme 1.5.1.

scheme 1.5.1.



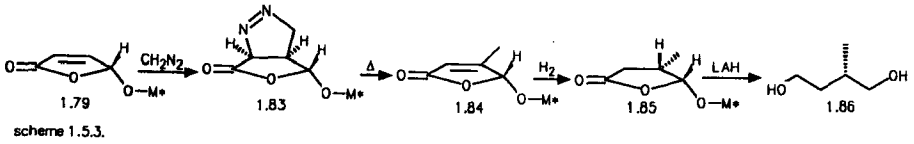
5(R)-(l-menthyloxy)-2[5H]-furanone 1.79

Sofar, asymmetric synthesis with **1.79** has mainly concentrated on cycloadditions and 1,4-additions; some representative examples are given:
i) Numerous Diels Alder reactions, of which one example is shown in scheme 1.5.2, have been studied by de Jong[71]. The products, such as the cyclopentadiene adduct **1.82** are obtained enantiomerically pure.



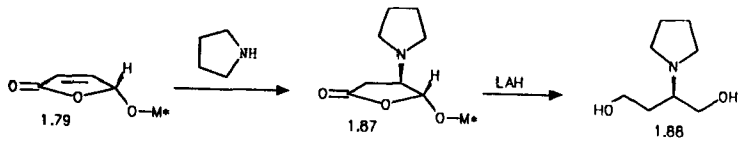
scheme 1.5.2.

ii) 1,3-Dipolar addition of diazomethane resulted in an efficient route to enantiomerically pure 2-methyl-butane-1,4-diols[72] such as **1.86** (scheme 1.5.3).



scheme 1.5.3.

iii) Compound **1.79** has been used by De Lange as Michael acceptor. Optically pure amino diols such as **1.88** were obtained from amino lactones **1.87** which were readily formed via diastereoselective additions of amines to **1.79**[73].(scheme 1.5.4)



scheme 1.5.4.

These auxiliary based enantiomerically pure synthons are to be preferred over sugar derived synthons for several reasons, for instance:

i) both enantiomers are available;

ii) the ease of preparation in multigram quantities;

iii) the possible recovery of the chiral auxiliary.

In this thesis the scope, use and limitations of 5(R)-(l-menthyloxy)- and/or 5(S)-(d-menthyloxy)-2[5H]-furanone as Michael acceptor will be discussed.

Due to the fact the substituent resides at the γ-position of the α,β-unsaturated lactone a nearly complete shielding of one of the π-faces with respect to the Michael addition can be expected.

The base catalyzed addition of carbon nucleophiles such as nitroethane and ethyl acetoacetate was studied first. The results of this study are described in chapter 2.

Next the addition of lithium enolates derived from esters such as α-methoxy ethyl acetate was studied (chapter 3). The stereochemical outcome with respect to the exocyclic stereogenic center was especially investigated. This investigation resulted in complete control, in several cases, over two newly formed stereogenic centers.

The lactone enolates that are formed after the initial addition of ester enolates can be

quenched in situ with electrophiles as is described in chapter 4. Quenching with methyl iodide resulted in control over a third new stereogenic center, whereas with benzaldehyde control over a fourth new sterogenic centers was possible.
Along with the introduction of ester substituents also alkyl substituents should be introduced (chapter 5). However, attempts to add organocuprates and organozincates failed. Introduction of alkyl substituents is possible via the addition of lithium bis-thiophenyl dithianes followed by a Raney Nickel reduction. Application of this concept to lignan synthesis resulted in the preparation of (-)-eudesmin.
In chapter 6 a survey of heteroatom based nucleophiles (O, P, N and S) and their 1,4-addition reactions with **1.79** is given.
As already mentioned, attempts to add organo zincates to **1.79** were unsuccesful. As a result of this study, the addition of organo zincates to cyclohexenone was also investigated (chapter 7). Especially the zincate mediated enantioselective 1,4-addition of Grignard reagents to cyclohexenone was studied.

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